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DIALOG(R)File 155:MEDLINE(R)
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09619548 98340238
Clinical experience with famciclovir against hepatitis B virus.
Bartholomeusz A; Groenen LC; Locarnini SA
Victorian Infectious Diseases Reference Laboratory, Fairfield, Vic., Australia.
Intervirology (SWITZERLAND) 1997, 40 (5-6) p337-42, ISSN 0300-5526 Journal Code: GW7
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
Famciclovir (FCV, the oral form of penciclovir, PCV) is a potent antiviral agent of hepatitis B virus (HBV) and is currently in phase III clinical trials. In this review, we examine the outcome of FCV treatment in preventing recurrent HBV in patients post transplantation. Resistance to FCV has now been documented in this setting, in which reduced sensitivity to FCV was associated with mutations upstream from the conserved 'YMDD' motif in the HBV polymerase gene. These mutations are in a region which has been designated as the B domain in RNA-dependent polymerases. To understand these mutations we have developed a model of the catalytic regions of the HBV polymerase and located mutations selected during antiviral treatment on this model. (40 Refs.)

6/7/2
DIALOG(R)File 155:MEDLINE(R)
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09619547 98340237
Experience with lamivudine against hepatitis B virus.
Jaeckel E; Manns MP
Department of Gastroenterology and Hepatology, Medizinische Hochschule Hannover, Germany.
Intervirology (SWITZERLAND) 1997, 40 (5-6) p322-36, ISSN 0300-5526 Journal Code: GW7
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
After several nucleoside analogues have been tested against chronic hepatitis B virus (HBV) infection with minimal success, lamivudine seems to be a highly effective new therapeutic option. This review focuses on nucleoside metabolism and on the molecular action of lamivudine as well as on results of clinical studies for several indications. We report on results of trials on the use of lamivudine for chronic HBV infection, chronic HBV under immunosuppression and prophylaxis or treatment of HBV reinfection before or after orthotopic liver transplantation. Aspects of combination therapy of different nucleoside analogues as well as on combination of lamivudine with interferon are also highlighted. Although lamivudine seems to be highly effective in most patients at the start of therapy, development of resistance by mutations in the viral polymerase is a significant clinical problem. The mode of resistance development is compared with the situation in HIV infection. Possible cross-resistance with other nucleoside analogues and the perspectives of lamivudine therapy are also considered. (117 Refs.)

6/7/3
DIALOG(R)File 155:MEDLINE(R)
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09278746 97331837
[Hepatitis B virus mutants--clinical significance]
Hepatitis-B-Virusmutanten--klinische Bedeutung.
Blum HE; Moradpour D; von Weizsacker F; Wieland S; Peters T; Rasenack JW
Abteilung Innere Medizin II, Medizinische Universitatsklinik Freiburg.
Zeitschrift fur Gastroenterologie (GERMANY) May 1997, 35 (5) p347-55, ISSN 0044-2771 Journal Code: XU1
Languages: GERMAN Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL; English Abstract
Hepatitis B virus (HBV) mutants have recently been identified in patients with acute or fulminant as well as chronic infections. Naturally occurring

mutations have been identified in all viral genes and regulatory elements, most notably in the genes coding for the structural envelope and nucleocapsid proteins. Mutations in the gene coding for the hepatitis B surface antigen (HBsAg) may result in infection or viral persistence despite the presence of antibodies against HBsAg (anti-HBs) ("vaccine escape" or "immune escape"). Mutations in the gene encoding the pre-core/core protein (pre-core stop codon mutant) result in a loss of hepatitis B e antigen (HBeAg) and seroconversion to antibodies to HBeAg (anti-HBe) with persistence of HBV replication (HBeAg minus mutant). Mutations in the core gene may lead among others to an "immune escape" due to a T cell receptor antagonism. Mutations in the gene coding for the polymerase/reverse transcriptase can be associated with viral persistence or resistance to nucleoside analogues. Thus, HBV mutations may affect the natural course of infection, viral clearance and response to antiviral therapy. Apart from the precore/core stop codon mutations, the exact contribution of specific mutations to diagnosis and therapy of HBV infection as well as patient management in clinical practice remain to be established. (79 Refs.)

6/7/4
DIALOG(R)File 155:MEDLINE(R)

09278570 97330388
Hepatitis B virus polymerase mutations during antiviral therapy in a patient following liver transplantation.
Aye TT; Bartholomeusz A; Shaw T; Bowden S; Breschkin A; McMillan J; Angus P; Locarnini S
Victorian Infectious Diseases Reference Laboratory, Fairfield Hospital, Melbourne, Australia.
Journal of hepatology (DENMARK) May 1997, 26 (5) p1148-53, ISSN 0168-8278 Journal Code: IBS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND/AIMS: The purpose of this study was to investigate possible resistance mutations which arose in the polymerase gene of hepatitis B virus (HBV) in a patient with severe recurrent HBV infection following liver transplantation. The patient's management included antiviral chemotherapy for almost 4 years comprising ganciclovir, foscarnet and famciclovir. In the last 2.5 years of famciclovir treatment, an increase in serum HBV DNA levels and a reduced sensitivity of the virion-associated DNA polymerase to penciclovir triphosphate were observed. METHODS: The viral polymerase gene and X gene were sequenced from serum samples collected at representative time intervals covering the entire treatment period. RESULTS: No mutations were detected in the X gene. Three nucleotide mutations, each of which resulted in an altered amino acid sequence, were detected in the polymerase gene after 816 days of total antiviral therapy (370 days of famciclovir). Two of these mutations were detected by direct sequencing and the third was detected after cloning and was present in 10% of the clones. All three mutations occurred in "region B" of RNA-dependent DNA polymerases. The HBV polymerase has similarities to both RNA and DNA polymerases. These mutations in the HBV polymerase gene were located in a similar area to the penciclovir-induced mutations observed in the herpes simplex virus DNA polymerase gene. CONCLUSIONS: Three mutations within the HBV polymerase gene were detected which were associated with a reduced penciclovir sensitivity.

6/7/6
DIALOG(R)File 155:MEDLINE(R)

09268098 97141868
Hepatitis-B-virus resistance to lamivudine given for recurrent infection after orthotopic liver transplantation [see comments]
Bartholomew MM; Jansen RW; Jeffers LJ; Reddy KR; Johnson LC; Bunzendahl H ; Condreay LD; Tzakis AG; Schiff ER; Brown NA
Division of Hepatology, University of Miami School of Medicine, Florida, USA.
Lancet (ENGLAND) Jan 4 1997, 349 (9044) p20-2, ISSN 0140-6736 Journal Code: L0S
Comment in Lancet 1997 Jan 4;349(9044):3-4
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: Orthotopic liver transplantation for end-stage hepatitis-B-virus (HBV) infection is commonly complicated by recurrence of HBV. Lamivudine, a cytosine nucleoside analogue, has been shown to suppress HBV infection. We report the development of resistance to lamivudine in three patients who underwent transplantation for end-stage liver disease secondary to hepatitis B. METHODS: Two of the patients received lamivudine for recurrent HBV infection after transplantation, whereas the third patient began treatment 1 month before transplantation in an attempt to prevent HBV recurrence after transplantation. The three patients initially responded well to treatment, but viral recurrence occurred after 9-10 months of treatment in all patients. HBV DNA was amplified from serum and sequenced through a conserved polymerase domain-the tyrosine, methionine, aspartate, aspartate (YMDD) locus. We assessed the susceptibility of HBV to lamivudine by infecting primary human hepatocytes with serum taken before the start of treatment and after recurrence in varying concentrations of lamivudine. FINDINGS: DNA sequencing showed a common mutation within the YMDD locus of the HBV polymerase gene in all patients during lamivudine treatment. In hepatocyte cultures infected with pretreatment serum, HBV DNA concentrations were reduced to less than 6% of those in control cultures by addition of lamivudine in concentrations as low as 0.03 mumol/L. By contrast, in cultures treated with serum taken after recurrence, HBV DNA concentrations did not fall below 20% of control values, even with lamivudine at 30 mumol/L. INTERPRETATION: Resistance to lamivudine has been reported in HIV patients with mutations in the YMDD locus of the polymerase

gene. Our findings indicate a common mechanism of lamivudine resistance for HIV and HBV that involves similar point mutations in homologous domains of the viral polymerases.

6/7/7
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09221385 97354334
Lamivudine resistance in immunocompetent chronic hepatitis B. Incidence and patterns [see comments]
Honkoop P; Niesters HG; de Man RA; Osterhaus AD; Schalm SW
Department of Internal Medicine II, Erasmus University Hospital Rotterdam, The Netherlands.
Journal of hepatology (DENMARK) Jun 1997, 26 (6) p1393-5, ISSN 0168-8278 Journal Code: IBS
Comment in J Hepatol 1998 Jan;28(1):169
Languages: ENGLISH
Document type: JOURNAL ARTICLE
BACKGROUND: Lamivudine is a non-toxic, potent inhibitor of hepatitis B virus replication. Recently, hepatitis B virus resistance to lamivudine has been described in patients using immunosuppressive drugs after liver transplantation. METHODS: From our cohort of 81 consecutive patients treated with lamivudine, we selected all immunocompetent patients who received lamivudine monotherapy for a period over 26 weeks (n=14). RESULTS: Lamivudine resistance with the characteristic mutation in the YMDD motif was observed in four patients (actuarial cumulative incidence: 39%). Two patterns of viral resistance were observed: incomplete response (n=2) and viral breakthrough (n=2). CONCLUSIONS: The observed high frequency of lamivudine resistance may have implications for the concept of long-term virus-suppressive therapy of chronic hepatitis B by lamivudine monotherapy.

6/7/10
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09006414 96374966
Mutation in HBV RNA-dependent DNA polymerase confers resistance to lamivudine in vivo.
Tipples GA; Ma MM; Fischer KP; Bain VG; Kneteman NM; Tyrrell DL
Department of Medical Microbiology and Immunology, Glaxo Wellcome-Heritage Research Institute, University of Alberta, Edmonton, Canada.
Hepatology (UNITED STATES) Sep 1996, 24 (3) p714-7, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The (-) enantiomer of 3'-thiacytidine (lamivudine) has been found to be a potent inhibitor of hepatitis B virus (HBV) and human immunodeficiency virus (HIV) replication. Mutation of methionine to valine or isoleucine at the YMDD (tyrosine, methionine, aspartate, aspartate) motif of the HIV reverse transcriptase has been shown to be responsible for lamivudine resistance in HIV. The hepadnaviruses also have the YMDD motif in their DNA polymerase. Therefore, it is possible that hepadnaviruses could develop lamivudine resistance by a similar mutation at this motif. We analyzed the HBV from a liver transplantation patient who developed recurrent HBV viremia during lamivudine treatment. The polymerase gene was amplified by polymerase chain reaction (PCR), and the region coding for the YMDD motif was sequenced. The pretreatment HBV sequence coded for YMDD, while the lamivudine-resistant mutant HBV coded for YIDD (tyrosine, isoleucine, aspartate, aspartate). With the documented changes in the YMDD motif of lamivudine-resistant HIV, it is likely that the methionine-to-isoleucine mutation in the YMDD motif of the HBV polymerase contributes significantly to the lamivudine-resistance of HBV isolated from this patient.

6/7/11
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09006413 96374965
Selection of mutations in the hepatitis B virus polymerase during therapy of transplant recipients with lamivudine.
Ling R; Mutimer D; Ahmed M; Boxall EH; Elias E; Dusheiko GM; Harrison TJ
University Department of Medicine, Royal Free Hospital School of Medicine, London, UK.
Hepatology (UNITED STATES) Sep 1996, 24 (3) p711-3, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We describe mutations in the hepatitis B virus (HBV) polymerase gene in viruses which reactivated in two patients during therapy with -2'-deoxy-3'-thiacytidine, or lamivudine (3TC), and following orthotopic liver transplantation for chronic hepatitis B. Virus resistance to 3TC is associated with mutations which lead to amino acid substitutions in the highly conserved tyr-met-asp-asp (YMDD) motif, part of the active site of the polymerase, and which parallel those seen in resistant human immunodeficiency virus (HIV). Substitutions of valine and isoleucine for methionine were found in the two cases. The significance of single secondary mutations, which differ between viruses from the two patients, remains to be determined. Thus, viral resistance to lamivudine of hepatitis B virus mimics that of HIV and can occur in the setting of immunosuppression after liver transplantations.

6/7/16
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08431224 96054949

Hepatitis B virus precore/core variation and interferon therapy.
Fattovich G; McIntyre G; Thursz M; Colman K; Giuliano G; Alberti A; Thomas HC; Carman WF
Istituto Semeiotica e Nefrologica Medica, University of Verona, Italy.
Hepatology (UNITED STATES) Nov 1995, 22 (5) p1355-62, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Precore/core genes from hepatitis B e antigen (HBeAg)-positive and antibody to HBeAg (anti-HBe) positive individuals with active hepatitis have been analyzed to search for correlations with response to interferon before and after treatment. Pretreatment, no precore stop codon mutants were detected, even at the 3% level, in HBeAg-positive responders or nonresponders. In anti-HBe-positive patients, precore mutants did not influence response. No significant core amino acid variability was observed in HBeAg-positive patients, irrespective of interferon response. However, anti-HBe-positive cases had multiple core protein substitutions, mostly in B- ant T-helper cell epitopes, but responders had fewer (P = .02 for responders versus nonresponders and reactivators). None of four responders, three of seven reactivators, and three of three nonresponders had mutations within the major T-helper epitope from aa50 to aa69 (P = .03). Precore mutants appeared in eight of nine natural seroconverters compared with 3 of 10 interferon-induced anti-HBe seroconverters (P = .01). Those in whom precore wild-type remained after treatment often tested negative in the last available sample using polymerase chain reaction (PCR), whereas emergence of mutants led to ongoing viremia in all cases. In anti-HBe-positive cases, precore sequences remained stable during therapy, except for 2 cases in whom a precore mutant appeared accompanied by reactivation. In the core protein, anti-HBe-positive cases selected a mean of 3.5, 1.6, and 1.7 amino acid substitutions in responders, nonresponders, and reactivators respectively (P = NS). In conclusion, core but not precore sequence before therapy may predict response. Appearance of precore mutants during therapy usually predicts failure to clear virus but substitution in core does not influence outcome.

6/7/21
DIALOG(R)File 155:MEDLINE(R)

07534817 93239103
Significance of pre-S region-defective hepatitis B virus that emerged during exacerbation of chronic type B hepatitis.
Minami M; Okanoue T; Nakajima E; Yasui K; Kagawa K; Kashima K
Third Department of Internal Medicine, Kyoto Prefectural University of Medicine, Japan.
Hepatology (UNITED STATES) Apr 1993, 17 (4) p558-63, ISSN 0270-9139 Journal Code: GBZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
A defective form of the hepatitis B virus has been found in a patient with chronic type B hepatitis. Sequence analysis of the viral DNA after polymerase chain reaction amplification revealed a 117-base pair deletion (nucleotides 3129-53, subtype adr). This deletion includes the initiation codon of the pre-S2 region and a newly created in-frame stop codon in the pre-S1 region (nucleotide 3055) located 230 base pairs downstream from the pre-S1 initiation codon. This virus coexisted with the wild-type virus during the exacerbation period, as evidenced by an elevation of serum transaminase levels. It was not detected in the stable period, and the blood chemistry results were normal. We assayed antibodies against the mutation-related region by enzyme immunoassay in serial serum samples to clarify the mechanism of the emergence of this variant virus. Antibodies against the pre-S2 region were negative; however, the antibody response against the pre-S1 epitopes coincided with the appearance of the variant virus. These findings suggest that an activated T-cell and B-cell response had developed against the pre-S1 region during hepatic inflammation in this patient and that, consequently, selection occurred for a pre-S antigen-defective mutant strain of the virus that might be resistant to such an immune response.
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